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Bimetallic catalysis by late transition metal complexes

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1. Introduction

Homogeneous catalysis is one of the most rapidly evolving areas of synthetic organic chemistry. There are strong incentives to achieve environmental friendly, high-economy processes and much research is performed to develop better and more selective catalysts.[1] Until now, the most selective catalysts are found in nature. Due to improved spectroscopic techniques, the elucidation of the structure of the active sites of many enzymes and the nature of the key intermediates in enzyme catalyzed processes have both contributed to dramatic progress in recent years. It has been shown that a number of these active sites contains two metal ions, that operate cooperatively.[2,3] As a result, dinuclear complexes containing two metals in close proximity have become the subject of extensive investigations in order to design new bimetallic catalysts.[3,4]

Complexes of interest for mimicking the activity of enzymes are especially dinuclear copper and iron compounds designed for reversible binding of dioxygen or activation of dioxygen. For instance, the dinuclear copper active site of hemocyanin[5] can reversibly bind dioxygen. The related enzyme tyrosinase[6,7] can activate dioxygen and hydroxylate monophenols to catechols and oxidize these catechols to *o*-quinones. Enzymes containing a dinuclear iron active site[8] are hemerythrin,[9] methane monooxygenase[10,11] and ribonucleotide reductase.[11,12] Hemerythrin is a dioxygen carrier and methane monoxygenase and ribonucleotide reductase activate dioxygen to hydroxylate methane to methanol and to generate a tyrosyl radical, respectively.

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Furthermore, many enzymes that contain two manganese ions in their active site have been discovered.[13] However, the mechanisms of these enzymes are until now poorly understood. The reactions that are catalyzed show wide variety, including several redox types, such as oxygen atom transfer, reduction of ribonucleotides to deoxyribonucleotides, or thiosulfate oxidation to sulfate in thiobacilli.

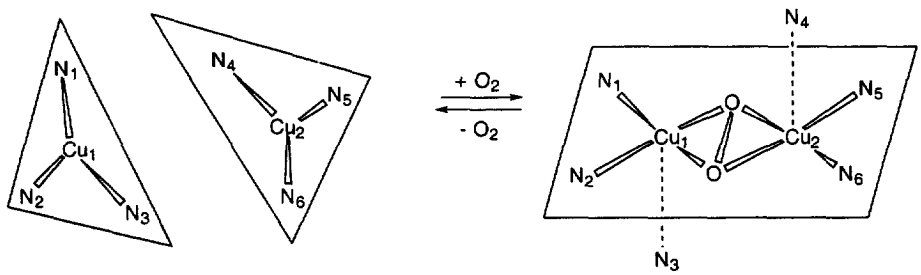
Attempts to mimic features of the active sites of these enzymes resulted in the awareness that two metals can cooperate in catalytic reactions and catalyze the reactions more efficiently or in a different manner when compared with two isolated metal centers.[14] Many dinuclear copper, iron, cobalt and manganese complexes have been synthesized successfully and several have shown a cooperative effect in the activation of dioxygen.[3] Moreover, synthetic dinuclear catalytic sites of transition metal complexes, which are not known to be present in dinuclear active sites of enzymes, have also shown cooperativity of the two metal centers during catalysis. Prominent examples are a dinuclear rhodium complex that has successfully been used in hydroformylation[15] of 1-hexene and a dinuclear palladium complex that catalyzes the hydration reaction of acetonitrile or related organic substrates.[16] For a better understanding of these processes, the study of the interaction of two metals in naturally occurring dinuclear sites (enzymes) and in synthetic dinuclear sites is required.

In this review, recent advances in the design, synthesis and application of dinuclear late transition metal complexes, that show promising bimetallic catalysis, will be discussed. First a brief summary of enzymes with dinuclear active sites which showed cooperativity of two metal centers is given to illustrate the principles which have evolved in nature. An in depth discussion of the bioinorganic aspects of dinuclear oxygenases is beyond the scope of this review.[2-14] Factors governing the design and synthesis of bimetallic catalysts are outlined. Furthermore the classification and characteristic features of various types of, so called, "two metal" or "two center" catalysis will be discussed. The major part of this review deals with recent examples of model systems for metallo-enzyme dinuclear active sites and catalytically active dinuclear complexes that clearly give enhanced reactivity or selectivity due to "bimetallic catalysis".

2 Naturally occurring dinuclear active sites

2.1 Dinuclear copper enzymes

Various enzymes with a dinuclear copper active site are known.[17] A well studied example is *hemocyanin* which functions as a dioxygen carrier in several species of the phyla *Mollusca* and *Anthropoda*.[5] The two copper ions are bound by three histidine imidazole ligands. Upon oxygenation the colorless protein becomes blue (hence *cyanin* from *cyanos*, Greek for blue). Recently, high resolution X-ray structures of hemocyanin from the anthropod *Limulus* in the oxygenated and deoxygenated form have been determined (Scheme 1).[18] In the deoxygenated form, the Cu···Cu distance is 4.6 ± 0.2 Å. In the oxygenated form a shorter Cu···Cu distance of 3.6 ± 0.2 Å is found. The closer Cu-Cu distance is presumably required to allow coordination of the oxygen molecule.

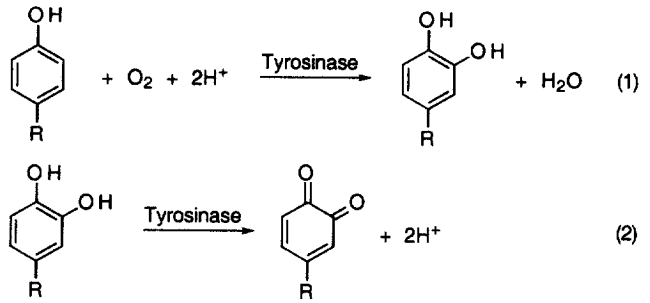


Scheme 1 Schematic diagrams of the deoxygenated (left) and the oxygenated (right) *Liminus* subunit II hemocyanin dicopper sites.[5]

The dioxygen binding of the two copper centers can be described as a change in the oxidation state of the copper ions from Cu(I) to Cu(II) as the dioxygen is bound as O_2^{2-} in a $\eta^2:\eta^2$ geometry.[5] In the deoxygenated state, each copper ion has a trigonal coordination provided by three histidine residues, consistent with the Cu(I) state. In the oxygenated form, the two copper atoms are coordinated by the two oxygen atoms and four nitrogen atoms of the histidines in an approximately square planar geometry.

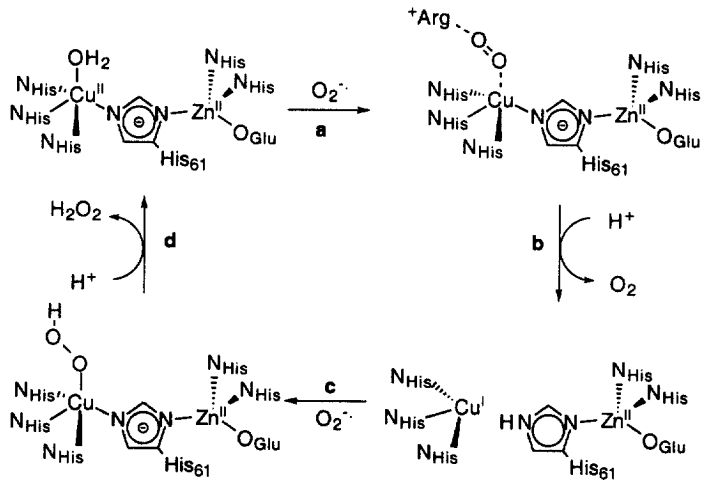
The hemocyanin dicopper sites are known to coordinate also other compounds besides dioxygen like nitrous oxide and hydrogen peroxide.

Tyrosinase is an enzyme that is closely related to hemocyanin and belongs to the class of monooxygenases.[6,7] Tyrosinase uses O_2 in the hydroxylation of phenols to catechols (cresolase activity; Scheme 2, reaction 1) and the further oxidation of these catechols to *o*-quinones (catecholase activity, reaction 2). The active site of tyrosinase consists of a similar structural unit to that found in hemocyanin, however, the copper centers are less protected by the protein environment.[19]



Scheme 2 Cresolase (1) and catecholase (2) activity of tyrosinase.

Another metalloenzyme, *superoxide dismutase*, contains two different metals in its active site: *i.e.* copper and zinc.[20] In the bimetallic region, the copper(II) center is coordinated in a square pyramidal geometry by four histidines and a water molecule. One of the histidines functions as a bridge to the zinc atom and is deprotonated. The zinc atom is further coordinated to two other histidines and one aspartic acid residue in an approximately tetrahedral geometry.

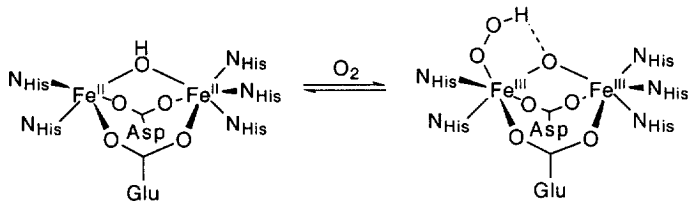


Scheme 3 Proposed mechanism for the catalysis of superoxide disproportionation by metalloenzymes.

Superoxide dismutase can destroy the highly reactive, destructive and toxic superoxide radical anion, $O_2^{-\cdot}$ to H_2O_2 and O_2. In the proposed mechanism (Scheme 3), the superoxide anion coordinates to the copper ion and to the guanine group of an arginine residue of another peptide chain (**a**). An electron is transferred to the Cu(II) center to form Cu(I) and dioxygen is released upon protonation of the histidine moiety (**b**). Next, a second $O_2^{-\cdot}$ binds to Cu(I) and is protonated (**c**). Transfer of one proton and one electron affords hydrogen peroxide and regenerates the Cu(II) ion (**d**). In this mechanism the zinc ion assists the protein to adopt the required coordination environment. However, it should be noted that there are ambiguities with respect to this mechanism. The turnover of the enzyme is too high for the involvement of protonation and deprotonation of the bridging histidine[21] and if the zinc ion is removed there is still dismutation however with only a limited turnover rate.[22]

2.2 Dinuclear iron enzymes

Hemerythrin[9] is well known for its function as a dioxygen carrier. The active center consists of two iron atoms roughly 3.25-3.5 Å apart, which are bound to the protein ligand by seven amino acid side-chain residues (Scheme 4). Three histidines bind to one iron and two histidines bind to the other iron. Glutamic acid and aspartic acid residues bridge the two metals. Furthermore, an oxygen atom derived from water is bound to both irons. EXAFS[23] and crystallographic studies[24] indicate that in deoxyhemerythrin the oxo bridge is protonated. The two iron atoms are in the Fe(II) state. Upon oxygen binding the colorless deoxyhemerythrin is converted to the purple oxyhemerythrin and the iron atoms are oxidized to Fe(III). At the same time, the proton from the hydroxide bridge migrates to the coordinated oxygen. Molecular oxygen is therefore bound as peroxide with a hydrogen bond to the bridging oxo moiety.



Scheme 4 Proposed active site structures of deoxyhemerythrin and oxyhemerythrin.

Methane Monooxygenase (MMO), which consists of three components: a hydroxylase, a reductase and a coupling protein, converts methane to methanol in a process that is coupled to the oxidation of NADH (Scheme 5).[11] The diiron site resides in the hydroxylase component (MMOH) and is responsible for oxygen activation and alkane hydroxylation.

$$CH_4 + O_2 + H^+ + NADH \longrightarrow CH_3OH + H_2O + NAD^+$$

Scheme 5 Oxidation of methane to methanol by MMO.

The crystal structures of both the oxidized[25] and the reduced form[26] of MMOH have been determined for the *Methylococcus capsulatus* enzyme (Fig. 1). The oxidized form contains a dinuclear Fe(III)-Fe(III) center. The two irons are bridged by a glutamate side chain, a hydroxide ion and an acetate ion from the crystallization buffer. The terminal ligands are two histidine nitrogens, three carboxylate oxygen donors and a water molecule which is hydrogen bonded to two carboxylate groups. Upon reduction of the dinuclear iron center to the Fe(II)-Fe(II) form, one specific ligand (Glu 243) undergoes a so called "carboxylate shift" from

monodentate terminal ligand to Fe2 to monodentate bridging ligand between the two irons. The other oxygen of the carboxylate group coordinates to Fe2 and the hydroxide bridge is lost. Only the reduced form reacts with dioxygen.

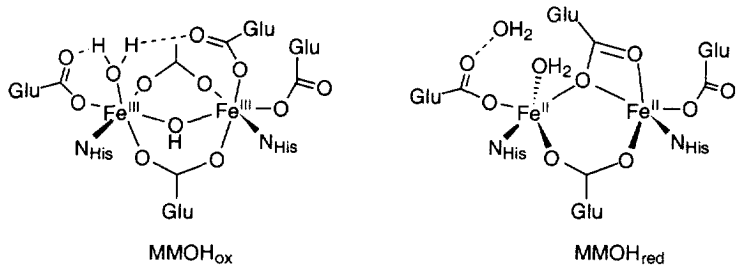
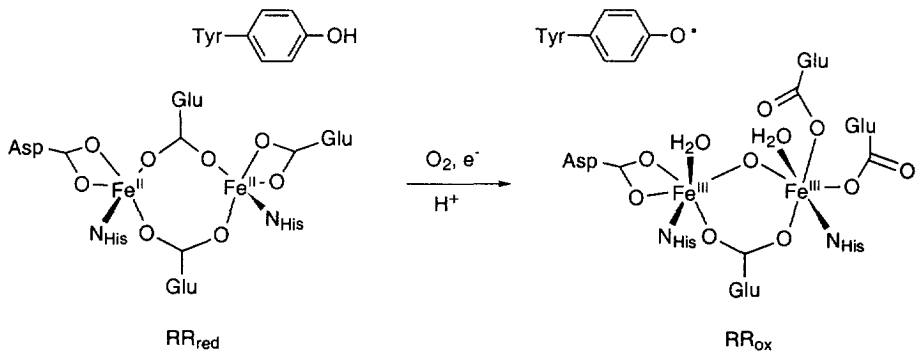


Figure 1 Structure of the active site of the oxidized and the reduced form of methane monooxygenase.[25,26]

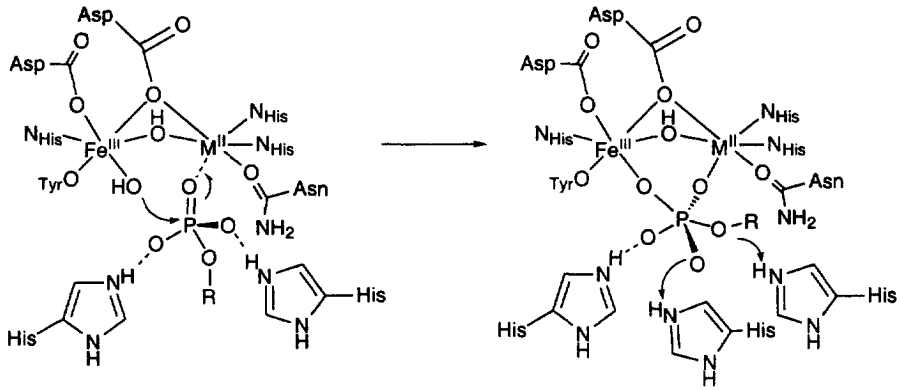
Ribonucleotide reductase (RR) is essential for the reduction of ribonucleotides to deoxyribonucleotides utilized in DNA biosynthesis.[11,12] The X-ray structures of the reduced and oxidized form are known and the initial part of the chemical transformation catalyzed by the enzyme is shown in Scheme 6.

The active site of the reduced form of ribonucleotide reductase contains two iron atoms bridged by two carboxylate groups. Furthermore there are two histidines coordinating to the dinuclear iron center and the remaining part of the coordination sphere is composed of carboxylate oxygen donor atoms. Interaction of the reduced form with oxygen generates, *via* two transient species, a tyrosyl radical and RR is converted to its oxidized form with an Fe(III)-Fe(III) oxo-bridge. The generated radical is responsible for the reduction of ribonucleotides. The exact mechanism of the subsequent steps has not yet been elucidated.



Scheme 6 Reaction of the reduced form of ribonucleotide reductase with O_2 to the oxidized form with concomitant formation of the tyrosyl radical.

Phosphohydrolases are known to have a dinuclear active site containing iron, zinc, manganese or magnesium and are capable of phosphate hydrolysis.[27] For instance, a dinuclear iron site is found in *mammalian purple acid phosphatases* (PAP) whereas the *kidney bean purple acid phosphatase* contains a heterodinuclear Fe(III)Zn(II) site. The PAP mediated hydrolysis occurs with inversion of the stereochemistry at phosphorus *via* a pentacoordinate intermediate, which is apparently stabilized by the metal ions and two histidines.[28] In the proposed mechanism, the phosphate ester is bound to M(II) [M(II) is Fe(II) or Zn(II)] and the Fe(III) bound hydroxide attacks the phosphate ester to form the intermediate (Scheme 7).



Scheme 7 Proposed mechanism for phosphate ester hydrolysis at the *kidney bean purple acid phosphatase* Fe(III)Zn(II) dinuclear site (M = Zn).

2.3 Dinuclear manganese enzymes

Compared to the copper and iron enzymes, dinuclear manganese enzymes have been explored less extensively and their mechanisms are still speculative. A summary of dinuclear manganese enzymes and their functions is given in Table 1.[13] In enzymes the oxidation states of manganese appear to be restricted to Mn(II), Mn(III) and Mn(IV). Probably, manganese centers with oxidation states higher than Mn(IV) are too powerful oxidizing agents and therefore unlikely to appear in biological systems. Reactions catalyzed by dinuclear manganese active sites are redox reactions, (de)hydrations, isomerizations, (de)phosphorylation and phosphoryl transfer.

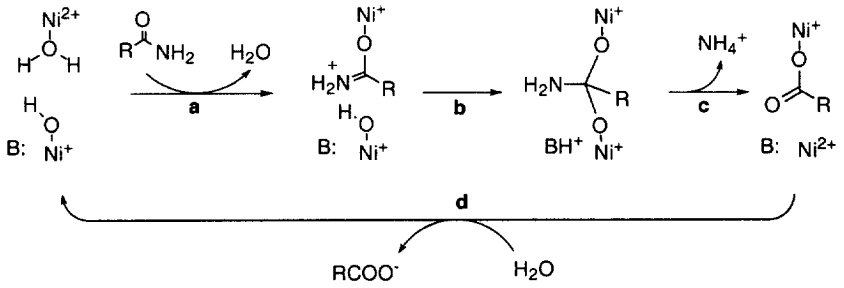
Table 1 Dinuclear manganese enzymes.[13]

enzyme	Mn-Mn site	reaction	enzyme reaction
arginase	Mn^{II}-X-Mn^{II}	arginine → urea + ornithine	hydration of guanidinium group
catalase	Mn^{II}-X-Mn^{II}, (3.6 Å)	$2H_2O_2 \rightarrow O_2 + H_2O$	redox, Mn^{II}, Mn^{III}
thiosulfate oxidizing	Mn^{II}-X-Mn^{II}	$S_2O_3^{2-} \rightarrow SO_4^{2-}$	presumably redox
ribonucleotide reductase	presumed dinuclear Mn^{III}-O-Mn^{II}	ribonucleotides → deoxyribonucleotides	tyrosine → tyrosyl radical
xylose isomerase	$Mn^{II}(RCO_2)Mn^{II}$, (4.9 Å)	glucose → fructose	1,2-keto-alcohol isomerization
ribonuclease H	$Mn^{II}(RCO_2)Mn^{II}$, (4 Å) Mg or Mn	RNA + H_2O → cleaved RNA	phosphodiester hydrolysis

2.4 Dinuclear nickel enzymes

Urease is an enzyme with a dinuclear nickel active site which catalyzes the hydrolysis of urea to ammonium carbamate.[27,29] The ligand environment of the nickel ions in the active site comprises nitrogen and oxygen ligands. The proposed mechanism[30] for the hydrolysis of urea is shown in Scheme 8.

The substrate (urea and a few substituted ureas and amides) binds to one nickel (**a**), which is followed by nucleophilic attack by hydroxide (**b**) that is bound to the other nickel center to form a tetrahedral intermediate. This step (**b**) is supported by a general base which is proposed to be a histidine.[27] An active site cysteine, which is known to be present in the enzyme but not as a ligand to nickel, is proposed to act as a general acid which promotes the release of ammonium ions (**c**) and the formation of a carboxylate or carbamate ion. Replacement of the coordinated carboxylate or carbamate ion by water leads to the regeneration of the initial state of the enzyme (**d**). Proper spatial orientation of the bound urea and the nucleophile and cooperation of the two nickel centers results in large rate enhancement for hydrolysis (10^{14}).



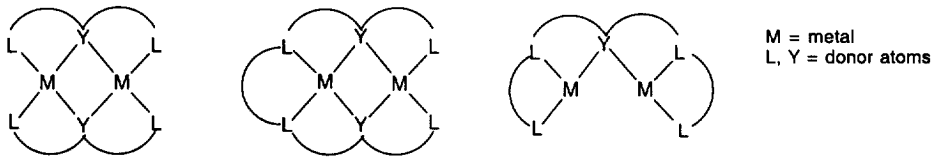
Scheme 8 Proposed mechanism for the hydrolysis of urea at the urease dinuclear nickel site.

Most of the enzymes that are briefly summarized here and which contain dinuclear active sites, show O_2 binding, oxygenase or hydrolase activity. In an efficient and also very elegant way two metals can cooperate in such diverse tasks as the activation of small molecules (O_2), selective conversion of notorious unreactive compounds (methane to methanol) or the dramatic acceleration of the hydrolysis of amide bonds under mild conditions. Although many mechanistic details of these conversions at the dinuclear sites need to be elucidated, it is clear that nature's principle of metal cooperativity offers a great challenge for the design of new 'bimetallic catalysts".

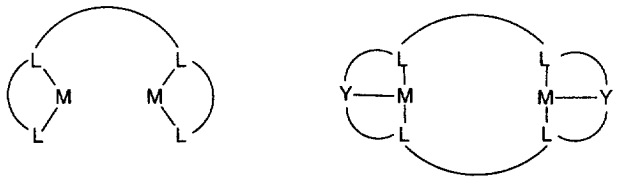
3 Synthetic dinuclear catalysts

3.1 Design of dinucleating ligands

For the synthesis of well defined dinuclear complexes, the choice of the ligand system is of major importance. In recent years investigations towards dinucleating ligands and related dinuclear complexes have increased significantly.[3] There are a number of requirements the dinucleating ligand has to satisfy. First of all, the ligand system has to be suitable to accommodate two metals. Moreover, the choice of the coordination environment (*i.e.* ligand effects like flexibility, steric, electronic, bridging ligand features, *etc.*) is very important because it determines the nature of the metal ions (type of metals, oxidation states, homo- or heterodinuclear) that can be bound. Finally, the metal-metal separation plays a crucial role in the activity of the designed complexes.
Dinucleating ligands can be divided into two classes (Fig. 2):[3d]
(*a*) Ligands which afford complexes in which the metal ions are sharing at least one donor atom. The ligands contain adjacent sites in which the central donor moiety provides a bridge between the metals. These ligands are termed compartimental ligands.
(*b*) Ligands which give rise to complexes in which donor atoms are not shared. In this case the donor sets are isolated.
It should be noted that the two metals in the dinuclear complexes (Fig. 2) can be the same (homodinuclear) or different (heterodinuclear).



Class (a) examples of dinuclear complexes of compartimental ligands



Class (b) examples of dinuclear complexes of ligands with isolated donor sets

Figure 2 Schematic representation of metal complexes of dinucleating ligands.

3.2 Reactivity of dinuclear catalysts

The catalytic activity largely depends on the structure of the complex.[31] The coordination environment does not only determine the nature of metal ions to be incorporated but also, amongst other features, the metal metal separation in the dinuclear complex.

The reactivity patterns of dinuclear complexes by which the two metals can cooperate are roughly divided into three classes (Fig. 3). In the first class (a), the substrate is coordinated to both metal ions simultaneously. In this way, the substrate can be activated and react with another molecule, either bound to a metal or unbound. In the second class (b), the substrate is bound to one metal center and the reactant to the other. Activation of the substrate and reactant can lead to bond formation of these two molecules. In most enzymes discussed in Section 2, these two pathways of activation are often combined in one catalytic cycle. In the third class, the second metal does not participate in the catalytic reaction, but helps to stabilize the reaction center for instance by donating or withdrawing electron density or by stabilizing a specific geometry at the dinuclear site. This cooperation is for instance proposed for the copper zinc dinuclear enzyme superoxide dismutase.

The optimum separation of the two metals appears to be 3.5 - 6 Å. Even if there is no direct interaction between the metal ions, the metals are still close enough to enforce the interaction of the substrate with both metals (*a*) or to bind two reactants in close proximity (*b*).

Finally, another basic requirement of the catalyst is that the product must be readily released from the dinuclear binding site.

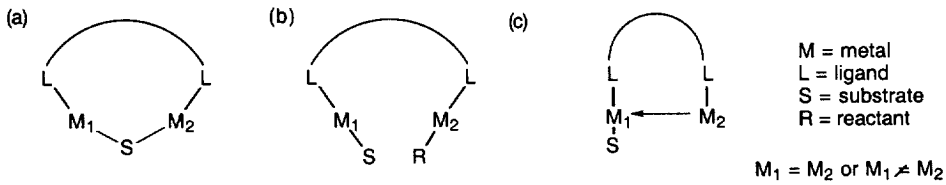


Figure 3 Schematic representations of possible cooperation of two metals in substrate (and reagent) activation.

3.3 Classification of dinuclear catalysts

A variety of possibilities can be conceived in which two metal centers can cooperate in catalytic conversions. The problems with a strict classification were recently outlined by Helmchen.[14b] Only a limited number of bimetallic catalytic systems are currently known and the precise role of the metals during the catalytic cycle is often not established.

A stringent definition of dinuclear catalysis is based on the cooperative effect of two metals (either the same or different) coordinated to the same ligand (Fig. 4, type A). The reactivity patterns were outlined in section 3.2.

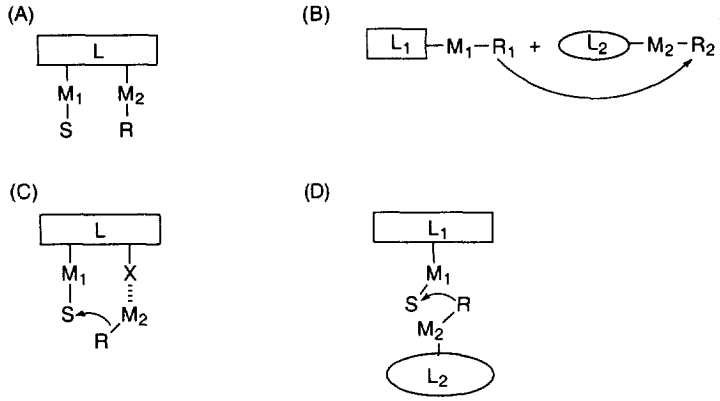


Figure 4 Types of bimetallic catalysis.

During dinuclear catalysis the substrate and reactant are bound and activated at the dinuclear center and the control of reactant and substrate geometry is often a key feature of these systems.

In a wider perspective many other forms of bimetallic catalysis can be envisioned. Two metals or complexes can effect each others reactivity by *in situ* dinuclear complex formation or aggregation. It is for instance well established that alkali metal ions can have a large effect on the reactivity and selectivity of cuprates.[32]

In enantioselective 1,4-additions of organometallic reagents to enones catalyzed by chiral copper complexes, dinuclear intermediates have been proposed in which the alkali metals serves either to control geometry or to act as a Lewis acid site.[33]

In type A catalysis, both metals are bound to the same ligand where the substrate is activated at M_1 and the reagent at M_2. A typical example is the hydrolysis of esters by phosphohydrolases already reported in section **2.2**. Mimics of these enzymes will be discussed in section 4.1.

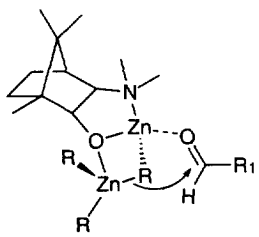


Figure 5 Proposed dinuclear zinc intermediate in the catalytic enantioselective addition of R_2Zn to aldehydes.

In type B catalysis or two component catalysis, one reagent is activated at M_1 and the other reagent at M_2. The bimetallic effect is merely the requirement of double activation for the reaction to proceed (section 8).
Several examples are known of type C catalysis in which a metal center (M_1) and a basic site (X) are present in the actual catalyst complex. Although there are two metals participating during the key catalytic step M_2 is provided by the stoichiometric reagent and replaced after the catalytic cycle. A typical example is found in the dinuclear zinc intermediate involved in the enantioselective 1,2-addition of organozinc reagents to aldehydes using chiral aminoalcohol ligands (Fig. 5).[34] In this particular case the "resting state" of the catalyst is also a dinuclear complex.
Type D catalysis combines aspects of type A and B catalysts in which two metal complexes not only activate their respective substrates (or a common one) but also assemble to form a bimetallic site in which both ligands participate to govern selectivity. Using this concept supramolecular catalysts have been developed.[35]

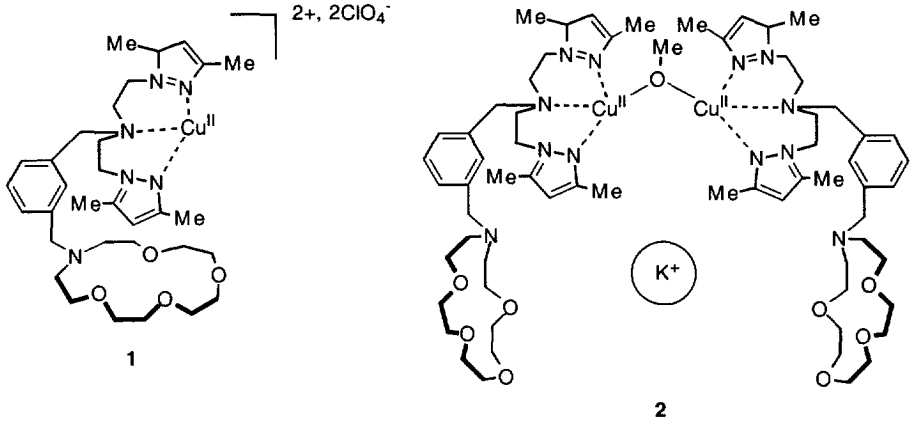
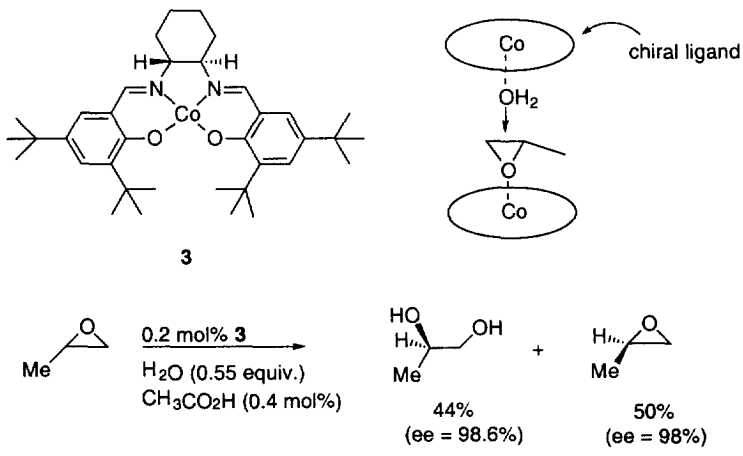


Figure 6 K^+ -induced assembly of methoxy-bridged dinuclear copper complex.

An illustrative example is found in the work of Nolte (Fig. 6).[36] Oxidation of methanol by the Cu(II)-complex **1** is accelerated in the presence of K^+-ions. This points to the formation of sandwich complex **2** and a mechanism involving a dinuclear alkoxy-bridged copper intermediate.



Scheme 9 Enantioselective "sandwich-type" two center catalysis.

Fascinating results in the kinetic resolution of epoxides, which apparently involve type D catalysis, have recently been reported by Jacobsen.[37] In the enantioselective hydrolysis of epoxides catalyzed by chiral cobalt salen complex **3**, ee's up to 98% have been obtained in the unconverted epoxide. As the reaction follows a second-order dependency on the concentration of **3**, the high selectivity might be attributed to two center catalysis; two molecules of **3** cooperate to activate both epoxide and water (Scheme 9). Similar bimetallic catalysts has been suggested for the ring-opening of epoxides by azides catalyzed by chiral chromium salen complexes[38a] and zirconium triisopropanolamine catalysts.[38b]
Finally it should be noted that in the literature a variety of terms including two center catalysis, bimetallic catalysis, bi- or di-nuclear catalysts, chemzymes, supramolecular catalysis, synzymes, have been used in cases where two metal centers cooperate in the catalytic cycle.

4 Model systems for metallo-enzyme dinuclear active sites

4.1 Dinuclear copper complexes

Functional model systems of enzyme active sites can be developed consisting of small, well defined molecules in order to mimic *e.g.* the formation of active intermediates, substrate binding and various aspects of the reactivity of enzymes. By mimicking the catalytic centers, it is possible to obtain more insight into the individual functions of certain groups in the enzyme with respect to the reaction mechanism. The information can then be used in the development of new synthetic catalysts.
Dinuclear copper complexes and their dioxygen binding are widely studied for this purpose in attempts to mimic hemocyanin and tyrosinase active sites.[3,39] The metal-dioxygen complexes found so far are very diverse in terms of structure, reactivity and spectral features and the different coordination modes are shown in Figure 7.

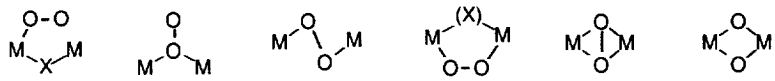


Figure 7 Coordination modes of dioxygen adducts adopted in dinuclear complexes.[39b]

Karlin and co-workers have developed a dinuclear copper complex, which is capable of binding dioxygen reversibly at low temperatures through formation of the deep purple compound **4** (Fig. 8).[40] Dioxygen is probably bound in a terminal way to one copper or alternatively in an unsymmetrical μ-1,2 mode to both coppers. The distance between the two copper centers is 3.3 Å. Furthermore, Karlin and co-workers described a mononuclear copper complex containing a tripodal tetradentate ligand, which underwent self-assembly to a dinuclear *trans*-μ-1,2-dioxygen complex **5** upon reaction with dioxygen at -80 °C.[41] The dioxygen binding of the copper complexes **4** and **5** is only reversible at low temperatures, which is strikingly different from the reversible room temperature dioxygen binding of hemocyanin. Other copper(I) complexes that have been reported to form dioxygen complexes in solution are also unstable in most cases.[42] However, recently an example of a dinuclear copper complex that is able to form a *trans*-μ-1,2-dioxygen complex at room temperature in protic media has been found by Reedijk and co-workers.[43]
A breakthrough in copper dioxygen binding was made by Kitajima and co-workers in their synthesis of complex **6**.[44] X-ray crystallography showed that dioxygen is coordinated in a μ-η^2:η^2-peroxo mode with a copper-copper distance of 3.56 Å. The spectroscopic characteristics of **6** closely resemble those observed for oxy-hemocyanin and after the discovery of **6** the X-ray structure of *Limulus Polyhemus* oxy-hemocyanin could finally be solved.[5]

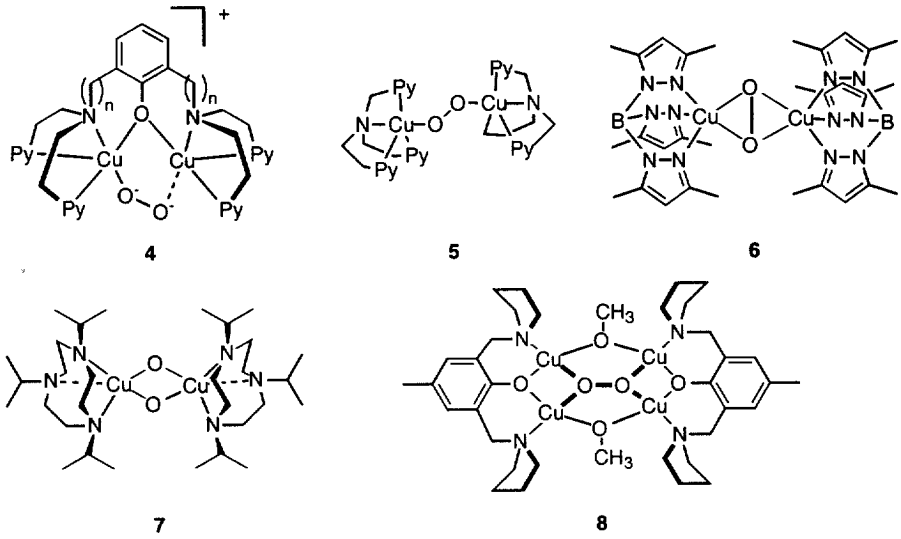
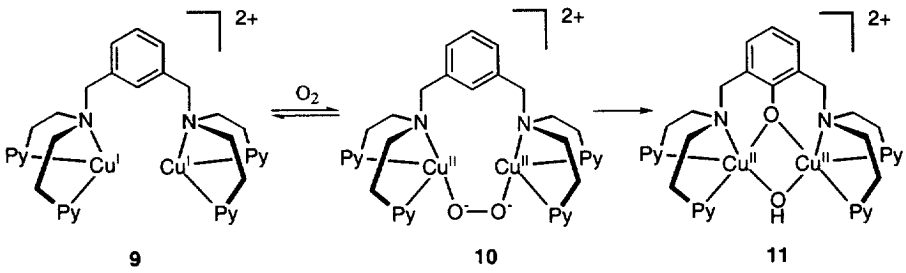


Figure 8 Dinuclear copper(II)-dioxygen complexes.

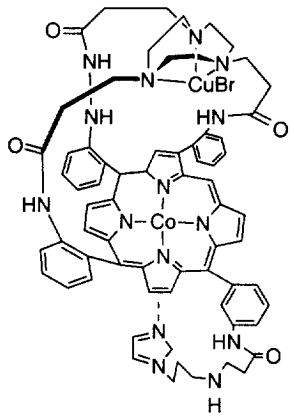
A new type of copper-dioxygen complex has been published by Tolman and co-workers.[45] This complex **7** contains a $Cu_2(\mu\text{-}O)_2$ core as found by X-ray crystallography. Important features are the copper-copper distance of 2.79 Å in **7** and the oxygen-oxygen distance of 2.28 Å, which are significantly different from the values found for the $Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)$ core (3.56 and 1.41, respectively). The synthesis of complex **7** containing a $Cu_2(\mu\text{-}O)_2$ core was performed in THF. By using CH_2Cl_2, a $Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)$ core was formed and interconversion between the two different oxygen binding modes was possible upon changing the solvent. The peroxo-copper complex **8** with an unsual μ_4 mode of coordination of the peroxo ligand has been reported by Krebs and co-workers.[46] In this complex the peroxo ligand is coordinated end-on in a fourfold bridging $\mu_4\text{-}(\eta^1)_4$ mode and lies above the Cu_4 plane. Another interesting structural feature is the ClO_4 unit (not depicted in structure **8**) which is situated below the Cu_4 plane with all oxygen atoms of ClO_4 indentically bound to all of the four copper ions.



Scheme 10 Tyrosinase model system.

Dinuclear copper complex **9** showed arene hydroxylation upon reaction with dioxygen to provide **11** (Scheme 10).[40] The reactivity of this copper complex resembles the reactivity of tyrosinase. Related work on O_2 binding with dinuclear complexes and oxygenation and mechanistic studies have also been reported from our group and by others.[47]

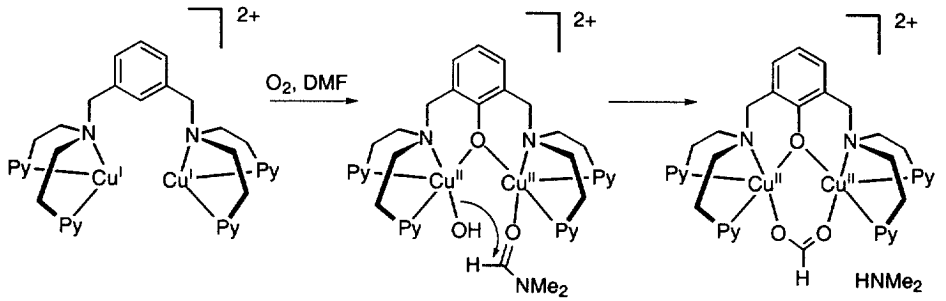
Recently, a heterodinuclear Co(II)-Cu(I) complex **12** has been reported by Collman and co-workers[48] as a model for the iron-copper bimetallic catalytic center of Cytochrome c oxidase (Fig. 9), which catalyzes the four electron reduction of O_2 to H_2O. This dinuclear complex consists of a cobalt porphyrin with a Cu(I) triazacyclononane attached at one side and an imidazole (as an axial ligand) on the other side of the porphyrin ring. The bimetallic complex strongly binds oxygen in a 1:1 stochiometry as indicated by IR and mass spectrometry. Furthermore, a four electron reduction of O_2 was observed at physiological pH.



12

Figure 9 Cytochrome c oxidase model system.

A few years ago, a biomimetic model system for amide hydrolysis was reported by Karlin and co-workers.[42b,49] Complex **9** reacts with dimethylformamide and oxygen instantaneously to form **14** (Scheme 11). In the postulated mechanism, the carbonyl group of the amide is activated by one copper center while a hydroxide is transferred by the second copper center as shown in structure **13**. Recently, Karlin and co-workers have reported on a dinuclear copper complex that is capable both of facile hydrolysis of unactivated esters and hydration of acetonitrile.[50]

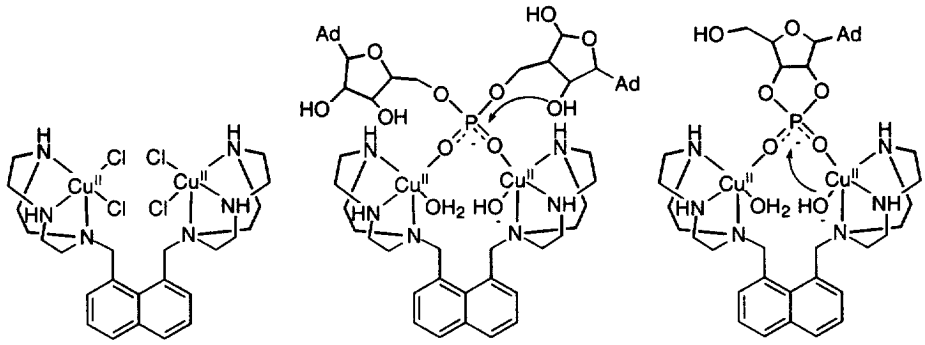


9 **13** **14**

Scheme 11 Biomimetic system for the hydrolysis of amides.

Dinuclear copper complex **15**, developed by Chin and co-workers, is capable of the hydrolysis of RNA (Fig. 10).[51] The cooperativity of the two metal centers is presumably due to bridging of the phosphate ester between the two copper centers as shown in **16**. This binding mode for a phosphate ester is also seen in previously

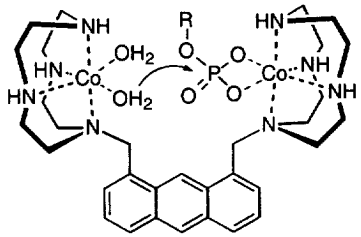
reported dinuclear copper and cobalt complexes.[52] In the proposed mechanism the 2-hydroxy group acts as an intramolecular nucleophile (see structure **16**). This is then is followed by hydrolysis of the cyclic phosphate ester by copper bound hydroxide (see structure **17**). The dinuclear copper complex is 300-500 times more active than the corresponding mononuclear complex (1,4,7-triazacyclononane)copper(II) dichloride.
Other approaches to supramolecular catalysts for hydrolytic reactions based on metalloaggregates, have been summarized by Feiters.[35]



15 **16** **17**

Figure 10 Hydrolysis of RNA by a dinuclear copper complex.

Finally in a related dinuclear cobalt complex **18**, reported by Czarnik and co-workers, the cooperative effect of the two metal ions results in a faster hydrolysis (approximately 10 fold) of phosphoric acid monoesters when compared with the mononuclear cobalt complex.[53] In the postulated mechanism, the phosphate is bound at one Co^{3+} center and the H_2O molecule is properly positioned for nucleophilic attack due to coordination to the second Co^{3+} center in a characteristic type A catalysis (Fig. 11).



18

Figure 11 Hydrolysis of phospohoric acid monoesters by a dinuclear cobalt complex.

4.2 Dinuclear iron complexes

The dioxygen activation by dinuclear iron active sites in enzymes is fascinating. While hemerythrin binds dioxygen reversibly, ribonucleotide reductase and methane monooxygenase bind dioxygen irreversibly and are capable of oxidizing tyrosine and hydrocarbons, respectively. Until now, only a few dinuclear iron model systems are known which bind (reversibly) dioxygen.

Que and co-workers have used the dinucleating ligand **19** with a 2-hydroxypropane backbone to prepare a dinuclear iron complex **22** (Fig. 12).[54] Complex **22** is able to bind dioxygen irreversibly by forming a 1:1 O_2 adduct. Suzuki and co-workers found that by using ligand **20**, the corresponding dinuclear iron complex binds dioxygen reversibly below -35 °C.[55] However, the related complex without the methyl groups at the 6-position of the pyridines binds dioxygen irreversibly. Probably, the 6-methyl groups introduce a steric effect that results in a shift of the Fe^{III}/Fe^{II} potentials to more positive values, thereby favouring an equilibrium between the deoxy and oxy forms.

Recently, Suzuki and co-workers have reported the dinuclear iron complex **22** derived from ligand **21**, which can form a very stable oxygen adduct **23**.[56] X-ray crystallography and Mössbauer data for this complex show two distinct high spin iron(III) centers, in which oxygen is bound in an *cis*-μ-1,2 mode. The two iron centers have a distorted octahedral coordination geometry. X-ray structure analysis of the dioxygen adduct of the dinuclear iron complex of ligand **19**, to which triphenylphosphine oxide was added to achieve stability, showed a similar *cis*-μ-1,2 mode of oxygen binding but did not show two different iron centers.[57] Another X-ray structure of a *cis*-μ-1,2 dioxygen adduct of a dinuclear iron complex has been reported by Kim and Lippard.[58]

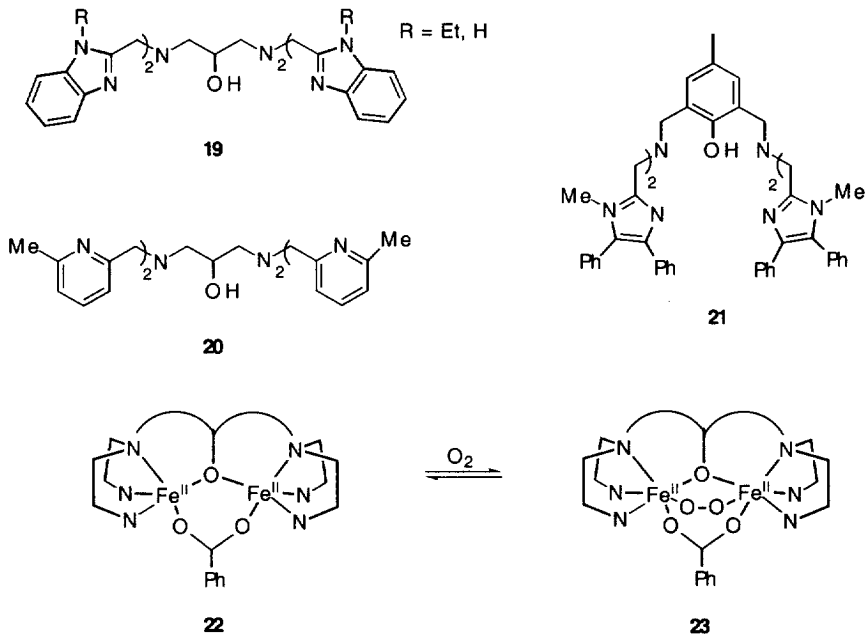
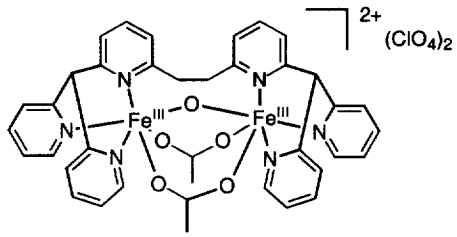


Figure 12 Dinucleating ligands and iron complexes capable to bind dioxygen.

A very reactive dinuclear iron complex **24** with a dinucleating hexapyridine ligand was published by Kodera and co-workers as a mimic for MMO (Fig.13).[59] This complex gave a very rapid functionalization of alkanes with *m*-chloroperbenzoic acid. For the conversion of cyclohexane to cyclohexanol, the system showed a high turnover frequency of 70 [mol product. mol catalyst^{-1}. min^{-1}] and a turnover number of 164 [mol product. mol catalyst^{-1}]. Other products formed during this reaction are cyclohexanone (68 turnovers), ε-caprolactone (48 turnovers) and chlorocyclohexane (12 turnovers). Upon renewed addition of *m*-chloroperbenzoic acid no loss of activity was found.

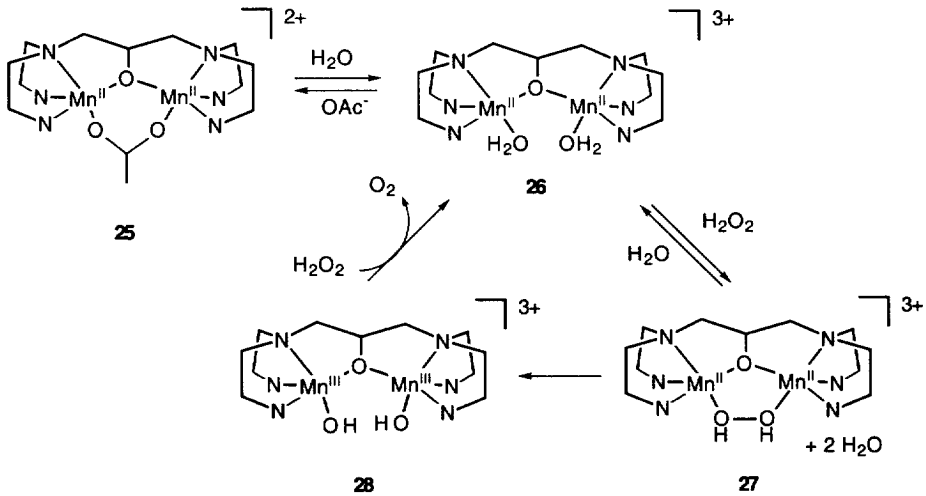


24

Figure 13 A dinuclear iron catalyst that shows MMO type activity.

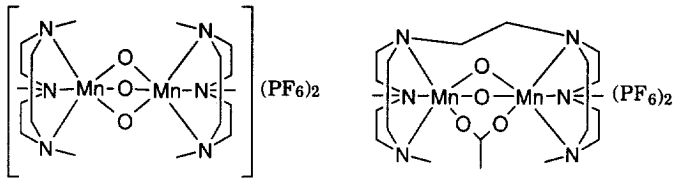
4.3 Dinuclear manganese complexes

The disproportionation of hydrogen peroxide into water and dioxygen is catalyzed by the enzyme catalase. A dinuclear manganese complex **25** based on heptadentate ligand **19** was reported by Dismukes and co-workers as a mimic for catalase.[60] In the postulated mechanism, dinuclear manganese complex **25** gives the "active" form of the Mn(II), Mn(II) catalyst **26** *via* an equilibrium with water, possibly by dissociation of the μ-acetate (Scheme 12). In the second step, hydrogen peroxide binds to **26** by displacement of bound water yielding **27**. This is followed by intramolecular electron transfer in which both Mn(II) centers are oxidized to Mn(III) with concomitant peroxide reduction to hydroxide leading to **28**. Subsequently reduction by a second peroxide molecule yields O_2 and restores the active starting material. A large variety of other dinuclear manganese complexes in various redox states have been prepared and structurally characterized for mimicking the structural and functional features of manganese enzymes. For instance a dinuclear complex, involving a peroxo-bridged $Mn^{IV}(\mu\text{-}O)_2(\mu O_2)_2Mn^{IV}$ dimer unit has been reported by Wieghardt and co-workers and proposed as a possible mimic for O_2 release in oxygen evolving systems in nature. Other dinuclear manganese biomimetic complexes have been reviewed by Que and True.[61] A recent review by Hage[62] gives a more detailed discussion of possible bimetallic catalysis by biomimitic manganese systems.[63]



Scheme 12 Proposed mechanism of catalase activity by dinuclear manganese complex **25**.

Several manganese complexes, **29** and **30**, based on 1,4,7-triazacyclononane (TACN) or bridged TACN ligands have been reported as excellent bleaching catalysts for detergent application (Fig. 14).[64] Furthermore epoxidation[65] and selective oxidation of alcohols to aldehydes[66] are highly effective with these catalysts. As the formation of mononuclear species **29** has been observed by EPR at pH<9.5 most probably the $Mn_2(\mu\text{-}O)_3$ core is not retained and bleaching involves mononuclear species at pH<9.5. At higher pH and with bridged complex **30** most probably bimetallic catalysis takes place.



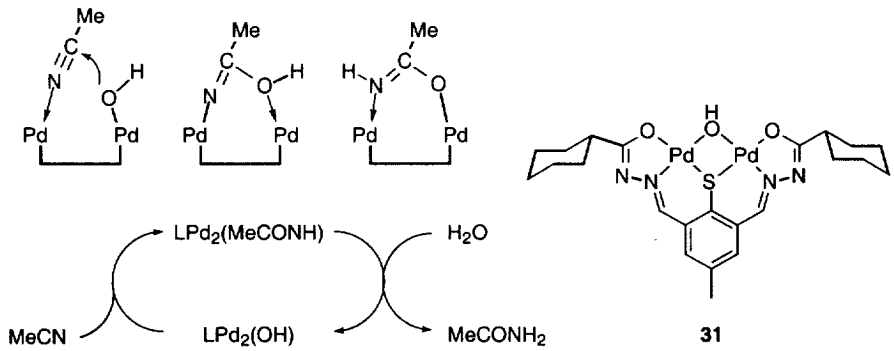
29 **30**

Figure 14 Dinuclear manganese complexes based on TACN ligands.

5 Dinuclear palladium catalysts

The dinuclear complexes which mimick enzyme active sites are often based on a compartimental ligand in which an oxygen bridges the two metal centers and holds them at a fixed distance from one another. Robson and co-workers used a related type of compartimental ligand containing a sulfur atom, which functions as a bridge between two metal centers. The dinuclear palladium complex **31** of this ligand catalyzes the hydration of acetonitrile to acetamide *via* a bimetallic pathway. The catalytic cycle starts with the coordination of acetonitrile to palladium (Scheme 13). Subsequently a carbon-oxygen bond is formed, to give the acetamide group which is coordinated to the two palladium centers. Finally, proton transfer and reaction with water yields acetamide. The cycle can be repeated upon binding of another acetonitrile molecule. The reaction was cocatalyzed by acid and turnover numbers of over 4000 moles were reached.[16]

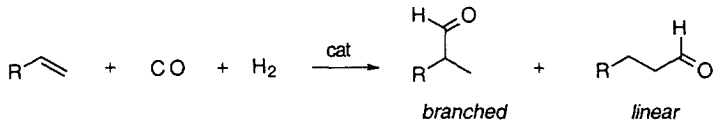
Support for the dinuclear mechanism was found on the basis of results of reactions carried out in basic medium, by employing a mononuclear palladium catalyst. In this catalytic cycle, the C-O bond is formed by nucleophilic attack of an uncoordinated hydroxide upon the coordinated acetonitrile.[67] However, the use of OH^- (1 equiv..) in the hydration reaction catalyzed by **31** decreased the rate by 80%, which therefore excludes a similar mechanism to that operating in the mononuclear catalyzed hydration.



Scheme 13 Proposed mechanism for the hydrolysis of acetonitrile catalyzed by dinuclear palladium complex **31**.

6 Dinuclear rhodium catalysts

An important breakthrough in dinuclear catalysis, not focusing on biomimetic systems, has been achieved by Stanley and co-workers with a dinuclear rhodium catalyst for the hydroformylation of α-olefins.[15] In the hydroformylation reaction, alkenes react with hydrogen and carbon monoxide to give either linear (*l*) or branched (*b*) aldehydes (Scheme 14). Dinuclear rhodium complex, *rac*-$[Rh_2(nbd)_2(et,ph\text{-}P4)]^{2+}(BF_4)_2$ (nbd = norbornadiene) **32** is a precursor for a highly active and regioselective catalyst in which the two rhodium atoms showed cooperativity of the two metal centers in the hydroformylation reaction (Fig 15). The hydroformylation of 1-hexene catalyzed by **32** is about 40% faster then the same reaction for the commercial Rh/PPh_3 catalyst and gives a high linear to branched aldehyde ratio (*l*/*b* = 28).



Scheme 14 Hydroformylation reaction of α-olefins.

It is proposed that the key step in the catalytic cycle is an intramolecular hydride transfer from one rhodium center to the other which contains the acyl chain, yielding the aldehyde. To verify this hypothesis of intramolecular hydride transfer, two ligands were prepared in which the rhodium atoms are unable to get close to one another. In complexes **33** and **34** the ethylene spacer is replaced by a rigid *p*-xylylene spacer and a more flexible propylene spacer, respectively. Furthermore, a mononuclear complex **35** was examined. All these models either do not catalyze the hydroformylation or catalyze the hydroformylation with very low activity. Recent *in situ* FTIR and NMR studies indicated that the mechanism is more complicated than initially proposed. The presumed active catalyst in the hydroformylation is based on complex **36** containing a unique Rh(II)-Rh(II) bond.[15b] This represents an 18-electron Rh(II) complex with an edge sharing bioctahedral structure, which is extremely rare. A feature of this complex is the very large $^1J_{Rh\text{-}H}$ coupling constant of 164 Hz.

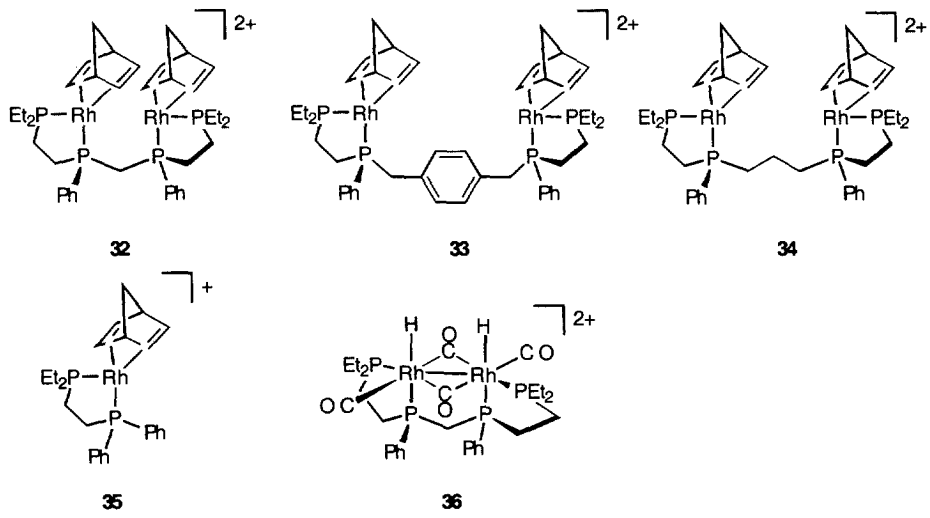


Figure 15 Mono- and dinuclear rhodium catalysts developed by Stanley and co-workers.

The high selectivity towards linear aldehydes is attributed to the rigid dinuclear structure of **36** and the favorable steric effects at the dinucleating phosphine ligand et,ph-P4. Coordination of an alkene to a typically mononuclear square planar rhodium phosphine catalyst causes the other ligands to bend away to form a trigonal bipyramid (or square pyramid). This reduces the steric effectiveness of the phosphine ligands for the insertion of the alkene in the rhodium hydride bond in such a way that the desired linear rhodium alkyl species is formed. In catalyst **36**, the alkene coordination cannot distort the steric effectiveness of the ligands since the Rh-Rh bond and the bridging carbonyls allow only a minimum of ligand reorganization. Due to the steric effect of the et,ph-P4 ligand, the alkene insertion in the M-H bond is directed to form a linear alkyl group resulting in a linear aldehyde.

Another type of dinuclear rhodium complexes, $Rh_2(\mu\text{-}SR)_2(CO)_2L_2$ (L = PPh_3) has been published by Kalck and co-workers.[68] It is proposed that these dinuclear rhodium complexes catalyze the hydroformylation reaction also *via* a dinuclear mechanism. Furthermore the same group found that di-μ-acetato-diruthenium complexes catalyze the hydroformylation of alkenes to aldehydes at low pressure (1MPa) with a remarkably high selectivity (Fig. 16).[69] Although different from the dinuclear rhodium system **32**, in the sense that an acetate bridge is present and no other dinucleating ligand, there seems to be a cooperative effect of the two Ru-centers. Most striking is the low hydrogenation activity of the dinuclear ruthenium catalyst. A catalytic cycle is proposed with a diacetato-bridged dirutheniumhydride $[L(CO)_2Ru(\mu\text{-}OAc)_2Ru(H)(CO)L]^-$ (l = phosphine) as the active species. Hydride transfer to the alkene, bound to the second Ru-center, takes place in the intermediate complex **37**.

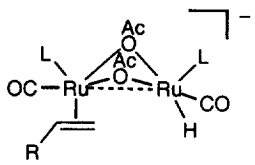


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Figure 16 Dinuclear ruthenium catalyst **37**.

7 Heterobimetallic systems

The cooperation of two metals in a heterobimetallic system is an attractive approach because the two metals can perform different tasks. Most often a hard and a soft metal are combined in one complex as the incorporation of a hard metal center, for instance a Lewis acid site, into a soft mononuclear transition metal catalyst may greatly alter the reactivity and selectivity. This has been demonstrated for Rh-Ti and Rh-Zr complexes in the hydroformylation reaction of olefins.[70] It is proposed that the reaction proceeds mainly *via* the rhodium center and that the second metal is able to increase or decrease the electron density at the rhodium center during the catalytic cycle. Another heterobimetallic complex which showed similar cooperativity is a compound of the type $[H(CO)(PPh_3)_2Ru(\mu\text{-bim})M(cod)]$ (bim = 2,2'-bisimidazolate, cod = 1,5-cyclooctadiene, M = Rh, Ir). These dinuclear catalysts show approximately 30 times higher activity in the hydrogenation reaction of cyclohexene than the parent mononuclear compounds $[RuH(Hbim)(CO)(PPh_3)_2]$ and [M(Hbim)(cod)].[71]

Kagan and co-workers and Jacobsen and co-workers have simultaneously published a chiral bimetallic catalyst **38** derived from modified diop (2,3-*O*-isopropylidene-2,3-hydroxy-1,4-bis(diphenyl)phosphino-butane).[72] The bimetallic complex contains a rhodium diphosphine unit, which acts as catalytic center in hydrogenation and hydrosilylation reactions and an arylboronic ester to function as a Lewis acid binding site for amines (Fig. 17). Binding studies showed that the rhodium boron dinuclear complex **38** can accommodate

amino olefins, as is illustrated in structure **39**, in which the two functionalities are at least 3 methylene groups apart.

The hydrogenation reaction of *N*-acetyldehydrophenylalanine and the methyl ester of *N*-acetyldehydrophenylalanine catalyzed by rhodium boron complex **38** gave high yields but was slightly less stereoselective than the hydrogenation with the mononuclear diop rhodium catalyst **40**. Also in the hydrosilylation reaction of ketones lower *ee*'s were obtained for the rhodium boron complex **38**.

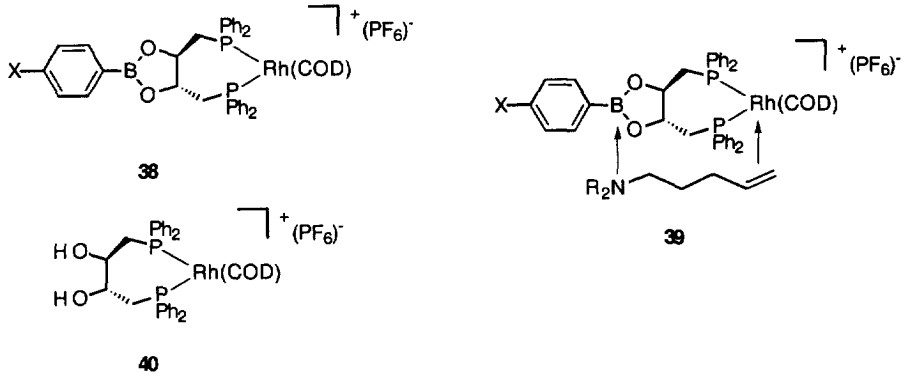


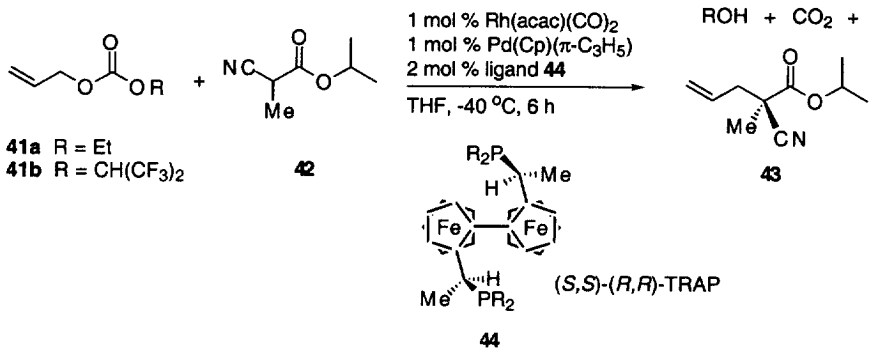
Figure 17 Bimetallic catalyst with a rhodium active site and a boron Lewis acid binding site.

In contrast to these results obtained with late transition metal complexes impressive results have been obtained by Shibasaki and co-workers with a new class of heterobimetallic compounds based on aluminium or lanthanides and alkali metals. The new catalysts consist of a central metal ion (*e.g.* La^{3+}, Al^{3+}), three alkali metal ions (*e.g.* Li^+, Na^+, K^+) and three molecules of 1,1'(*R*)- or 1,1'-(*S*)-binaphthol (BINOL). In the asymmetric nitroaldol addition with a LaLi-BINOL compound as catalyst up to 94% enantiomeric excess and 90% yield were obtained.[73] In the asymmetric hydro-phosphonylation reaction of imines and aldehydes, a LaK-BINOL catalyst gave enantiomeric excesses up to 96% with yields of 70%.[73c] Furthermore, in the Michael addition, the highest enantiomeric excess (95% *ee*, quantitative yield) was achieved with a LaNa-BINOL catalyst.[74] Mechanistic studies showed that the lanthanide functions as a Lewis acid center to activate the enone as well as to control the geometry of the coordinated enone.

8 Two-component catalyst systems

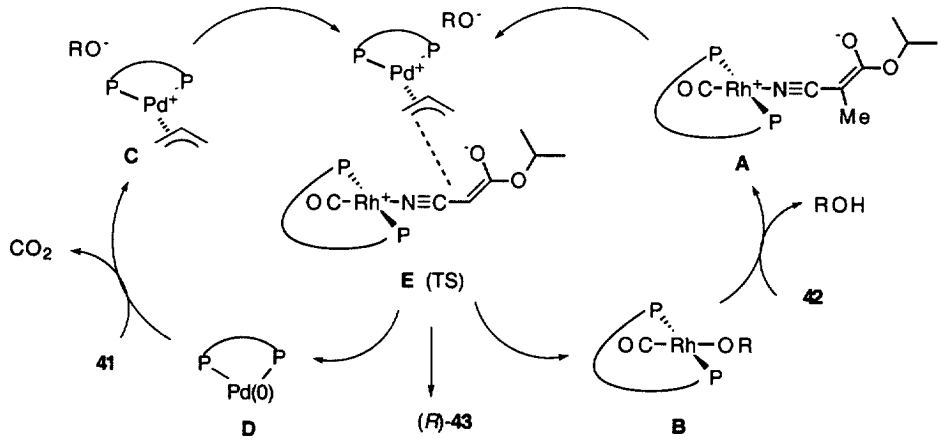
Two-component catalyst systems consist of two different transition metal complexes, in which the two catalysts activate their respective substrates resulting in a more active system when compared with the mononuclear complexes. Hidai and co-workers have reported several bimetallic catalysts including a $Co_2(CO)_8$-$Ru_3(CO)_{12}$ system for the hydroformylation of olefins[75] and the $PdCl_2(PPh_3)_2$-$Ru_3(CO)_{12}$ system for formylation of aryl iodides and vinyl iodides which are twice as active as the mononuclear analogs.[76] In the proposed mechanism, the synergistic effects are explained by dinuclear reductive elimination reactions between acylcobalt or acylpalladium intermediates and hydridoruthenium to give the corresponding aldehydes. Based on the same principle a Pd-Co system was developed for the carbonylation of aryliodides with $HSiEt_3$.[77]

Recently, Sawamura, Sudoh and Ito reported an impressive example of a two component rhodium palladium catalyst.[78] The *trans* chelating bisphosphine ligand (S,S)-(R,R)-TRAP was applied in combination with $Rh(acac)(CO)_2$ and $Pd(Cp)(\pi\text{-}C_3H_5)$ in the enantioselective allylic alkylation of α-cyano esters (Scheme 15).



Scheme 15 Enantioselective allylic alkylation of an α-cyano ester promoted by a two-component Rh-Pd catalyst and a chiral ligand.

The proposed mechanism is shown in Scheme 16. The π-allylpalladium complex[79] **C** can be produced from TRAP, an allylic carbonate and a catalytic amount of a palladium complex. The rhodium-enolate complex **A** is initially formed from $Rh(acac)(CO)_2$, TRAP and cyanoester **42**. Nucleophilic attack of the enolate **A** on the π-allylpalladium complex **C** proceeds *via* transition state **E** and produces (*R*)-**43** in high yields (84-98%) and with an enantiomeric excess up to 99%. During this step, the palladium(0) complex **D** is regenerated and the alkoxide (RO^-) becomes a ligand for rhodium to form alkoxy rhodium(I) complex **B**. When in this reaction palladium was omitted, no conversion was observed after 24 h. Conversily, when rhodium was left out, high yields were obtained but no enantiomeric excess was found. These results together demonstrate the unique cooperative features of this system.



Scheme 16 Proposed mechanism for the enantioselective allylic alkylation catalyzed by a two-component Rh-Pd system.

9 Conclusions

Considerable progress has been seen in recent years in approaches to bimetallic catalysis and some remarkable discoveries of enhanced selectivity and/or activity show the potential benefits of dinuclear catalysts. A number

of dinuclear complexes have been investigated in order to activate small molecules. It is evident that dioxygen binding with synthetic dinuclear copper and iron systems has considerable impact on our understanding of dioxygen binding in natural systems. Furthermore copper, iron, cobalt and manganese complexes have shown interesting catalysis in attemps to design mimics of enzymes. The cooperativity of the two rhodium atoms observed in the hydroformylation reaction demonstrates that dinuclear catalysis might provide new opportunities for many other areas of catalysis not related to enzymic mimics. In heterobimetallic systems, an enhancement of the activity can be obtained by using a second metal which can control electron density at the catalytic center. Self-assembly of bimetallic sites during the catalytic event holds great promise to enhance selectivity in catalysis. Finally, two-component systems, based on two different transition metal complexes, have shown cooperativity during the catalytic cycle. For instance, a two-component rhodium palladium system gave excellent catalytic activity with high enantioselectivity in the alkylation of activated nitriles. These two component systems can be used in future for the design of new dinuclear catalysts.

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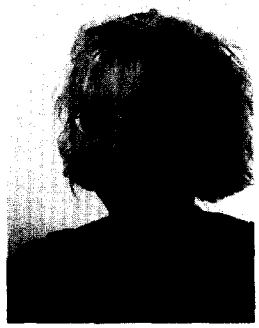
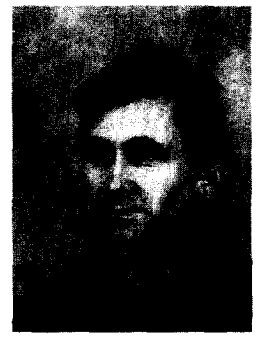
Biographical sketch



Esther K. van den Beuken



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Esther van den Beuken was born in 1969 in Prinsenbeek. She studied chemistry at the University of Nijmegen (1987 - 1992). In 1993 she started her PhD research with Prof. Dr. B.L. Feringa at the University of Groningen on the topic of Mono- and Dinuclear Transition Metal Complexes based on Phosphorus and Nitrogen Ligands. She obtained her PhD degree in June 1997 and since July 1997 she is employed by Fuji Photo Film in the Netherlands.

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